REMARKS

Amendment to the Specification

The second sentence of the second paragraph on page 3 has been amended to correct a grammatical error. No new matter has been added.

Claim Status

Claims 82-94 are pending. Claim 82 is amended herein. Support for this amendment is found in the specification at e.g., page 3, ll. 7-14; p. 3, ll. 35-39; p. 27, l. 33 to page 28, l. 31 (human anti-gp39 antibodies); p.14, ll. 19-21 and p. 28, l. 24 to p. 29, l.6 (mouse anti-gp39 antibodies).

Rejections Under 35 U.S.C. §112-Written Description and Enablement

The Examiner has rejected the claims for allegedly lacking sufficient written description and enablement. According to the Examiner, the claimed antigen as described by its properties is not sufficiently precise to establish that the inventors had possession of the claimed invention or to enable one of ordinary skill in the art to practice the claimed method.

To expedite prosecution, claim 82 has been amended to specifically recite that the method comprises using both an antigen-presenting cell that presents an autoantigen to an activated T cell expressing mouse or human gp39; and an anti-gp39 antibody which binds to mouse or human gp39 on the activated T cell. gp39 is fully disclosed in the specification, for example, via incorporation by reference of Hollenbaugh et al., *EMBO J.*, 11:4313-4319 (see the specification at p. 2, l. 30, and p. 7 l. 8 and ll. 12-13).

Specifically, the present specification and the state-of-the-art make it clear that gp39 is found only on **activated** T cells as shown by the following excerpts:

> The specificity of the selected antibodies was conformed by several assays. First, flow cytometric analysis demonstrated that 4D9-8 and 4D9-9 stain activated but not resting peripheral blood T cells (see Figure 9) (specification, page 3-5 and Figure 9) .

Hollenbaugh (attached as **Exhibit 1**) also explicitly discloses that gp39 is expressed on activated T cells (emphasis supplied):

> Recently, it has been shown that the ligand for CD40 is a cell surface protein of approximately 39 kDa expressed by **activated** T cells, gp39 (see abstract).
>
> We and others have used soluble forms of the extracellular domain of CD40, CD40-Ig, to show that the CD40 ligand gp39 is a glycoprotein of ~ 39 kD expressed on the surface of **activated** CD4+ murine T cells.. (see p. 4313, col.2, 2nd ¶).

See also Figure 2, (1992) of the Hollenbaugh reference which discloses the nucleotide and amino acid sequences of murine and human gp39. The remainder the article further describes additional physical and functional characteristics of gp39.

Lastly, U.S. 6,403,091 to Lederman (cited by the Examiner) also notes that gp39 is expressed only on activated T cells.

> This invention provides a monoclonal antibody which specifically recognizes and forms a complex with T-B cell activating molecule (T-BAM) (now also known as CD40 ligand) a protein located on the surface of **activated** T cells and thereby inhibits T cell activation of B cells (see first sentence under "Summary of the Invention").

The specification also demonstrates that the inventor has possession of the claimed invention. The Examples demonstrate use of both anti-human gp39 and anti-mouse gp39, in conjunction with antigen-expressing APCs, to reduce responsiveness of T cells against the specific antigen expressed by the APCs upon re-challenge with the antigen. Reduced T cell responses to the antigen which are exemplified include reduced proliferation (Examples 1 and 2); reduced ability to mount primary and secondary CTL responses (Example 3), and treatment/prevention of

GVHD in vivo in response to bone marrow transplants as evidenced by reversal of splenomegaly, inhibition of IgE, hyper-Ig, and anti-DNA autoantibody production (Example 5).

In view of the foregoing, it is submitted that the claims are sufficiently described and enabled. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103(a)-Obviousness

The claims stand rejected as unpatentable over Lederman et al., U.S. Patent No. 6,403,091 ("Lederman"), in view of Beschorner et al., U.S. Patent No. 5,597,563 ("Beschorner"), Cobbold et al., U.S. Patent No. 5,690,933 ("Cobbold"), and Enyon et al., *J. Exp. Med.* 175: 131-138, 1992 ("Eynon"), and additionally, U.S. Patent No. 6,264,951 ("Armitage"), and U.S. Patent No. 6,376,459 ("Aruffo").

Specifically, the Examiner contends that there would have been sufficient motivation to combine the teachings of the foregoing references to arrive at the claimed invention with a reasonable expectation of success, and that such a combination teaches each and every limitation of the claims.

In view of the present amendment, the rejection over Armitage and Aruffo should be withdrawn since the claims no longer refer to CD40-Ig fusion proteins or soluble CD40L. Accordingly, withdrawal of this rejection is respectfully requested.

Regarding the Examiner's remaining rejections (Lederman in view of Beschorner, Cobbold or Eynon), it is respectfully submitted that none of the remaining cited references in combination teach or suggest all of the limitations of the claimed method for reducing antigen-specific T cell responsiveness *in vivo* to an autoantigen presenting cell (APC) by administration of **both**: (1) an antigen-presenting cell that presents an autoantigen to an activated T cell expressing mouse or human gp39; ***and*** (2) an anti-gp39 antibody which binds to mouse or human gp39 on the activated T-cell, and wherein the anti-gp39 antibody is administered prior to, concurrent with, or

subsequent to administration of the antigen-presenting cell in an amount effective to reduce T cell responsiveness to the antigen-presenting cell (see amended claim 82).

As noted by the Examiner, Lederman does not teach the administration of APCs (Office Action, dated October 22, 2002, p. 3, ¶ 2). While Beschorner discloses the administration of APCs which present an antigen for inducing tolerance to self- or auto-antigens, this is done in an environment *devoid* of activated T cells (i.e., subsequent to the use of a general immunosuppressive agent). According to Beschorner, the effects of the immunosuppressant are measured by evaluating the increased levels of cortical thymocytes, i.e., immature T cells expressing both CD4 and CD8, in the blood (as released by the thymus). Such immature thymocytes are not ordinarily present in the peripheral blood, because they normally develop into *either* CD4+ or CD8+ T cells in the thymus, where they then encounter antigen and undergo thymic selection prior to being released into the blood to carry out their immune function (Beschorner, col. 5, ll. 11-13, col. 7, ll. 3-5, and col. 8, ll. 3-13).

Moreover, in order for T cells to become "activated" in the thymus, contact with an APC (harboring an antigen) is required. Since Beschorner's immunosuppressant also depletes the thymus of endogenous APCs (prior to administration of his exogenous APCs; see col. 5, ll. 12-17), any already-mature T cells present in the thymus at the time of immunosuppressant administration cannot become activated.

Thus, it can be established that administration of an immunosuppressant as taught by Beschorner depletes the thymus of both mature, activated, T cells, and any T cell pre-cursors. The former cannot become activated, and the latter are prematurely released from the thymus prior to activation.

In view of the foregoing, Beschorner teaches away from the present claims, which depend on blocking interaction with an activated T cell, and is therefore unavailable for use in an obviousness rejection.

Cobbold discloses only the co-administration of anti-CD4 and anti-CD8 monoclonal antibodies in order to induce T cell tolerance and prevent skin graft rejection (Cobbold, abstract, col. 3, ll. 15-16 and ll. 39-47). Cobbald makes no mention of anti-gp39 antibodies much less co-administration of antigen presenting cells with the antibodies. To the contrary, Cobbald explicitly states that the skin graft itself provides the source of the antigen, not exogenously administered APCs (see col., 15, ll. 39-47). Accordingly, since Cobbald discloses neither of the limitations presently claimed (no administration of an APC and no administration of an anti-gp39 antibody), Cobbald could not be combined with Lederman to teach each and every claim limitation. Lederman does not remedy the deficiency since Lederman discloses using *only* an anti-gp39 antibody but does not disclose this use in combination with an APC (see col. 8, ll. 5-5; col. 9, ll. 36-38; col. 10, ll. 14-16 and 28-30; and col. 11, ll. 8-13, etc.).

Moreover, there would have been no motivation to combine Lederman and Cobbald since Lederman states that his anti-gp39 antibody acts to block the "effector" phase, which is T cell-induced differentiation of B cells into Ig-secreting cells, while an anti-CD4 antibody blocks the "inductive phase", which is the initial physical interaction of a T cell with a B cell (which comes *prior* to the effector phase; see Lederman at col. 1, ll. 28-42). Since Cobbald's method is already blocking the physical interaction of a T cell with a B cell (the "inductive" phase), there would have been no motivation for one of ordinary skill in the art to look to Cobbald for guidance when attempting to block the subsequent "effector" phase. If the teachings of Cobbald are believed, there should be no effector phase to block following use of an anti-CD4 antibody.

Even improper combination of Cobbold with Lederman *still* would not result in each and every limitation of the present claims since neither reference teaches co-administration of their respective antibodies with an APC as presently claimed.

Eynon discloses presentation of antigen by a B cell to a "small resting T cell" and "unprimed T cells"—not T cells expressing mouse or human gp39 (Eynon, p. 131, col. 2, ¶ 1, p. 135, col. 2, ¶ 1). Moreover, Eynon discloses administering only an antigen to induce T cell

tolerance-there is no mention of administering an APC, much less together with an anti-gp39 antibody which targets activated (not resting) T cells.

First, Eynon does not disclose administering an APC, but instead relies on a population of endogenous APCs (small resting B cells) to process the antigen and present it to un-activated T cells. In addition, the precise antigen used by Eynon (monovalent, ultracentrifuged Fab anti-δ Ig fragments) was pre-selected for its known specific ability to be taken up and presented by small resting, IgD-expressing B cells. Eynon acknowledges that this method is expected to be effective only for antigens that are self-Ig isotypes and for self-proteins not expressed in the thymus (p. 136, col. 2, last ¶). Moreover, the tolerance induced by this method was transient (see p. 136, col. 1, second ¶). This transience would be quite useless in e.g., an autoimmune or transplant context as the present inventions seeks to address.

The only administration of an APC disclosed by Eynon is in the context of testing whether T cell tolerance was induced by her method, which involves taking T cells out of the mouse who was administered the antigen and putting them into SCID mice along with normal B cells to see if the T cells could activate B cells. However, this is not a method of *inducing* tolerance, but a method of *evaluating* whether tolerance has occurred.

Second, there would have been no motivation to combine Eynon with Lederman since Eynon depends on inducing tolerance by contacting a small resting T cell with a small resting B cells. As has been established by the citations above, only activated, not resting, T cells express gp39.

In fact, Eynon's method of self-tolerance is hypothesized to be due to the *lack* of co-stimulation (i.e., engagement of gp39) as indicated by the following:

> As outlined above, the interaction of an antigen-specific resting T cell with an antigen-specific resting B cell may be ineffective [at activating a B cell to produce antibodies] due to a **lack of co-stimulator** signal or signals.....(p. 132, col. 1, end of first ¶)

Although this sentence is in reference to prior work done using antigen-specific B cells as APCs, this mechanism was the basis for Eynon's study, since Eynon's method also depends on the use of *unactivated* B cells presenting antigen to *unactivated* ("naïve") T cells (see p. 132, col. 1, second ¶) This makes perfect sense given the fact that resting T cells lack gp39, and thus, lack the ability to become "co-stimulated" and in turn, activate B cells.

In short, Eynon's disclosure is irrelevant to examination of the presently claims which are directed to a method of co-administering an anti-gp39 antibody along with an APC to induce T cell tolerance to an antigen. Any combination with Lederman does not remedy this deficiency, since Eynon's method of tolerance does not involve any administration of an APC, and Lederman's method also does not involve any administration of an APC. Moreover, since Eynon's method does not involve blocking the co-stimulatory signal to an activated T cell (as the T cells she uses do not become activated) the two references are inapposite and cannot properly be combined to render an obviousness rejection.

Accordingly, withdrawal of this rejection is respectfully requested.

In view of the above amendment and remarks, Applicant believes the pending application is in condition for allowance and such action is earnestly solicited.

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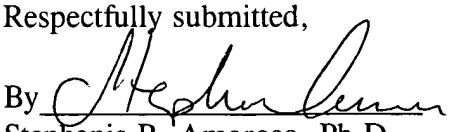
Respectfully submitted,

By 

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